REMARKS

Favorable reconsideration is respectfully requested in view of the following comments.

Upon entry of these amendments, claims 1- 8 and 11-13 will be pending, of which claims 1 and 12 are independent.

The proposed amendments to claims 1 and 3 (changing "in solution" to "dissolved") merely make explicit what was believed to have been at least fully implicit, namely that the amount of 6-APA in solution refers to dissolved 6-APA. References to "dissolved" 6-APA are found throughout the specification, e.g., page 2, lines 23-26, page 4, etc.

Claim 1 is also amended to clarify that the batch process is carried out under the conditions i), ii) and iii), wherein, in i) the total concentration applies substantially throughout the reaction while ii) applies throughout the reaction. This clarification should provide the additional clarity requested by the Examiner regarding the "timing" for the amounts/ratios as set forth.

Claim 7 is amended as proposed by the Examiner.

As such, no new matter is added by the claim amendments, nor do the amendments change the scope of the claims.

Claim 11 is directed an embodiment wherein the total concentration applies throughout the reaction, e.g., wherein the total amount of 6-APA is present in the reaction mixture at the start of the reaction. Claim 13 is similarly directed to this embodiment.

Claim 12 is directed to another embodiment, substantially identical to claim 1, except that the condition ii), that the amount of dissolved 6-APA is kept lower than 300 mM throughout the process is deleted. In this regard, as shown in "Comparative

Experiment A" (which does not represent the prior art) and Graph 2, based thereon, with the amount of dissolved 6-APA at the early stage of the reaction higher than 300 mM, the production of AMPI is still high with the first and third conditions satisfied.

Accordingly, one skilled in the art reading the disclosure would recognize that Applicants were in possession of the subject matter of claim 12 at the time this application was filed.

Therefore, claim 12 does not introduce new matter into the Application and is supported by the written description.

The rejection of claims 1-10, under 35 USC 112, second paragraph, as confusing regarding the stage of the reaction for which the stated amounts are required, is respectfully traversed for at least the following reasons.

Condition i) recites that the total concentration of 6-APA and ampicillin (AMPI) is the total concentration (dissolved and undissolved) in the reaction mixture (as stated in the original claim language; see also page 3, lines 7-10). However, the total concentration need not be greater than 250 mM for the entire reaction. For instance, as explained on page 4, lines 16-18, it is within the scope of the invention to initially charge only part of the total quantity of 6-APA and add the rest during the reaction. Accordingly, claim 1, recites "substantially throughout the reaction."

Regarding, the Examiner's question concerning the measurement of total amounts of reactant and product, the Examiner's confusion is not understood. Certainly, since product may be formed throughout the course of the reaction its concentration may change throughout the reaction. Similarly, the amount of reactant, being consumed and or added during the course of the reaction, may change throughout the course of the reaction. Nevertheless, this does not preclude taking a sample at any particular time and measuring the amount of 6-APA and ampicillin in

the reaction mixture. This is precisely what is shown in the graphs appended to the application. Techniques for measuring concentrations of 6-APA and AMPI are well known in the art, for example, as shown in WO '061.

For condition iii) the ratio refers to the total quantity of PG derivative added to the reaction mixture (before and during the reaction) divided by the total of 6-APA added to the reaction mixture (before and/or during the reaction) (see, e.g., page 3, lines 15-20). As suggested, the word "added" is deleted.

It is respectfully submitted that the claims are neither unclear nor indefinite.

Claims 9 and 10 are cancelled, thus obviating the rejection as applied to these claims. Applicants do not abandon the subject matter of these claims.

Accordingly, the rejections of claims 1-10 under 35 USC 112, second paragraph, are respectfully traversed.

The claims stand rejected under 35 USC §103 as being obvious over WO 92/01061 (WO '061) taken with WO 95/03420 (WO '420). Applicants respectfully traverse this rejection for at least the following reasons.

WO '061 nowhere describes a solution concentration, i.e., dissolved amount, of 6-APA, lower than 300 mM. Similarly, WO '420, nowhere describes the dissolved concentration of 6-APA being lower than 300 mM. Accordingly, the combined disclosures of the references must also fail to disclose this feature of the present invention.

Therefore, no proper case of *prima facie* obviousness has been established in the record. Accordingly, Applicants request withdrawal of this rejection of claims 1-10.

The objective of WO '061 is to obtain high conversion with respect to 6-APA. This high conversion is, however, accomplished only at the expense of low conversion of the acylating agent (phenylglycine derivative). Such low conversion is a disadvantage since large amounts of reactants need to be recovered and/or are lost.

Operating under the conditions disclosed in this reference, it is not possible to achieve both high conversion of phenylglycine (PG) derivative and high conversion with respect to 6-APA.

More particularly, from the examples in WO '061 which are related to production of ampicillin (as shown in the following table) the conversion with respect to 6-APA varies between 60% and 98% and the conversion with respect to PG derivative varies between 11% and 34%.

Table: examples of WO'61 relating to the preparation of ampicillin (AMP)

Example	Initial conc. 6-APA	Initial conc. PG Deriv.	Ratio k	Total conc. 6-APA+AMP	Conversion of 6-APA	Conversion of PG Deriv.
	mM	MM		mM	(%)	(%)
1 (1st)	100	270	2.7	<100	74	27
1 (2nd)	100	750	7.5	<100	98	13
3 (pH=3)	250	700	2.8	<250	60	21
3 (pH=6.4)	250	700	2.8	<250	94	34
3 (pH=7.0)	250	700	2.8	<250	93	33
4 (T=10 C)	180	700	3.9	<180	95	24
4 (T=20 C)	180	700	3.9	<180	96	25
4 (T=35 C)	180	700	3.9	<180	60	15
5 (1st)	100	270	2.7	<100	74	27
5 (2nd)	100	750	7.5	<100	86	11
6	150	700	4.7	<150	90	19
7	230	920	4	<230	91	23

As may easily be appreciated from the above table, the ratio k is always greater than 2.5 and the total concentration of 6-APA and PG derivative is always less than 250 mM.

For ease of comparision, the following table summarizes results from the specification of the subject application.

Application	Added 6-APA	Added PG Deriv.	Ratio k	Total conc. 6-APA+AMP	Conversion of 6-APA	Conversion of PG Deriv.
	Mmol	Mmol		mM	(%)	(%)
Example II	600	1000	1.67	>400	96	58
Exp. A	600	950	1.58	>400	92	58

For clarity, it is explained that "conversion" of 6-APA and of PG derivative, is based on the yield of ampicillin (AMP) relative to the total amounts of 6-APA and PG derivative. Thus, in the case of Example II (page 10) the total amount of 6-APA was 600 mmol and the total amount of PGA was 1000 mmol. Therefore, since 575 mmol of AMP was formed the conversions of 6-APA and PGA, are, respectively, (575/600) X 100 and (575/1000) X 100.

It will be recalled that in Experiment A conditions i) and iii) were both satisfied. A high PG derivative conversion (58%) was achieved, even though condition ii) specifying the low concentration of dissolved 6-APA was not satisfied (during the early part of the experiment the concentration of dissolved 6-APA was higher than 300 mM). This is shown in Graph 2.

When condition ii) (as in Example II) is also satisfied, the conversion for 6-APA increases from 92% to 96% while still maintaining high PG derivative conversion.

These conditions and results are not suggested in the disclosure of WO '061. In fact, considering the results from Example 1 (1st) and Example 1 (2nd) wherein the ratio k increased from 2.7 to 7.5 whereas conversion of 6-APA increased from 74% to 98%, one skilled in the art would expect that at low k values only low 6-APA conversions would be obtained. See also the results from Examples 5 (1st) and (2nd) where similar results were obtained.

As noted from the specification, e.g., page 2, line 23 to page 3, line 2, when working at high total concentration of 6-APA and ampicillin combined and a low molar ratio of the total quantity of added phenylglycine derivative to the total quantity of added 6-APA (below 2.5), the conversions of 6-APA and PG derivative, may be unexpectedly increased. In addition to high conversions of both 6-APA and PG derivative, stirrability of the reaction may be also improved when the conditions ii) is satisfied.

Since there is no suggestion in the disclosure of WO '061 to operate at the conditions specified in the present claims and, certainly, no motivation to operate at a k ratio > 2.5, and at a total concentration of 6-APA and ampicillin smaller than 250 mM, much less at the totally undisclosed low concentration of dissolved 6-APA (as opposed to undissolved/solid 6-APA) the present invention, including claims 11-13, as well as claims 1-10, would not have been *prima facie* obvious over the cited references.

With regard to WO '420, Applicants note that this reference is directed to recovering the phenylglycine derivative from the reaction mixture and not to improving the reaction conversions. Therefore, WO '420 does not provide motivation to obtain the present invention. Still further, this reference teaches that the concentrations of reactants used by this process are not critical (*see* page 1, lines 10-15). Thus the skilled artisan is afforded no reasonable expectation of success in obtaining better reaction conditions by the general reagent recovery technique described by this reference.

In any case, the disclosure of WO '420, is relied on only with respect to the feature of claim 7, but fails to obviate the deficiencies of the primary reference WO

'061. Therefore, the combination of these disclosures, even if proper, which is not conceded, would not render the present invention *prima facie* obvious.

CONCLUSION

In view of the above amendments to the claims and the foregoing remarks, the Applicants respectfully assert that all of the Examiner's objections and rejections have been overcome. Accordingly, early and favorable notice of allowance of the present application with claims 1-13 is respectfully requested.

Respectfully submitted,

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Enclosure: Appendix

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

1. (Three times Amended) A batch process for preparation of ampicillin comprising:

a) acylating 6-aminopenicillanic acid (6-APA) with a phenylglycine derivative in the presence of an enzyme to form a reaction mixture;

wherein the process is carried out under the following conditions:

i) the total concentration in the reaction mixture of 6-APA and ampicillin combined is, substantially throughout the reaction, greater than 250 mM;

ii) the concentration of dissolved 6-APA [in solution] is lower than 300 mM throughout the reaction; and

iii) the molar ratio of the total quantity of [added] phenylglycine derivative to the total quantity of [added] 6-APA is less than 2.5.

2. (Twice Amended) Process according to Claim 1, wherein the total concentration of the 6-APA and ampicillin present in the reaction mixture is, substantially throughout the reaction, greater than 300 mM.

3. (Twice Amended) Process according to any one of Claims 1 or 2, wherein the concentration of dissolved 6-APA [in solution] is kept lower than 250 mM throughout the reaction.

4. (Three times amended) Process according to claim 1, wherein the molar ratio of the total quantity of phenylglycine derivative [employed] to the total quantity of 6-APA is less than 2.0.

7. (Twice Amended) Process according to Claim 6, wherein the phenylglycine derivative is metered in the form of a solution of D-phenylglycine amide.1 2 H_2SO_4 in water.

Claims 11-13 are added.